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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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Ex parte EBRAHIM ZANDI and BETH SCHOMER MILLER

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Appeal 2010-012363  
Application 10/079,949  
Technology Center 1600

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Before TONI R. SCHEINER, DONALD E. ADAMS, and  
JEFFREY N. FREDMAN, Administrative Patent Judges.

FREDMAN, Administrative Patent Judge.

DECISION ON APPEAL<sup>1</sup>

This is an appeal under 35 U.S.C. § 134 involving claims to a method of preparing an active IKK protein complex. The Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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<sup>1</sup> The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing, as recited in 37 C.F.R. § 41.52, begins to run from the “MAIL DATE” (paper delivery mode) or the “NOTIFICATION DATE” (electronic delivery mode) shown on the PTOL-90A cover letter attached to this decision.

## Statement of the Case

### Background

“Under normal circumstances, the NF-κB transcription factor is tightly regulated to allow an appropriate and rapid response to infection or stress while preventing an inappropriate inflammation from a false trigger” (Spec. 1, ll. 17-19). According to the Specification, in “resting cells, NF-κB is found predominantly in the cytoplasm in a complex with IKK, an inhibitory subunit, which sequesters NF-κB and prevents its migration to the nucleus” (Spec. 2, ll. 18-20). The Specification teaches that “[d]iverse stimuli lead to phosphorylation of two serine residues [which] frees NF-κB to move to the nucleus where it binds with high affinity to κB elements in the promoter region of target genes” (Spec. 2, ll. 20-23).

### The Claims

Claims 2, 5-7, 17-19, 21-23, and 42 are on appeal. Independent claims 2, 23, and 42 are representative. The remaining claims have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Independent claims 2, 23, and 42 read as follows:

2. A method for preparing substantially homogenous, biologically functional and activated IKK protein complex comprising transforming a yeast with an IKK subunit gamma ( $\gamma$ ) gene and an IKK subunit alpha ( $\alpha$ ) gene and an IKK subunit beta ( $\beta$ ) gene and growing said yeast and separating said IKK protein complex from said yeast thereby preparing substantially homogenous, biologically functional and activated IKK protein complex.

23. The method of claim 2 or 42, wherein one or more of said IKK subunit ( $\gamma$ ) gene, or IKK subunit ( $\alpha$ ) gene or IKK subunit ( $\beta$ ) gene encodes a mutated IKK subunit protein.

42. A method for preparing substantially homogenous, biologically functional and activated IKK protein complex comprising transforming a yeast with an IKK subunit gamma ( $\gamma$ ) gene and an IKK subunit alpha ( $\alpha$ ) gene and an IKK subunit beta ( $\beta$ ) gene and growing said yeast and separating said IKK protein complex from said yeast, wherein the IKK protein complex is autophosphorylated at a T loop of an IKK subunit beta ( $\beta$ ) thereby preparing substantially homogenous, biologically functional and activated IKK protein complex.

#### The issue

The Examiner rejected claims 2, 5-7, 17-19, 21-23, and 42<sup>2</sup> under 35 U.S.C. § 103(a) as obvious over Rothwarf,<sup>3</sup> Traincard,<sup>4</sup> and Epinat<sup>5</sup> (Ans. 5-9).

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<sup>2</sup> We treat the absence of claim 42 from the grounds of rejection on page 5 of the Answer as a typographical error since the claim was listed in the Final Rejection mailed Sep. 2, 2009 and is separately discussed in the Answer (see Ans. 3, 14-15).

<sup>3</sup> Rothwarf et al., IKK- $\gamma$  is an essential regulatory subunit of the I $\kappa$ B kinase complex, 395 NATURE 297-300 (1998).

<sup>4</sup> Traincard et al., Evidence for the presence of an NF-kB signal transduction system in Dictyostelium discoideum, 112 J. CELL SCIENCE 3529-3535 (1999).

<sup>5</sup> Epinat et al., Reconstitution of the NF- $\kappa$ B System in Saccharomyces cerevisiae for Isolation of Effectors by Phenotype Modulation, 13 YEAST 599-612 (1997).

The Examiner finds that “Rothwarf et al. teach the coexpression of human IKK $\alpha$ , IKK $\beta$  and IKK  $\gamma$  genes in a eukaryotic host by inserting the genes encoding each subunit fused to a tag (HA or FLAG) into a mammalian expression vector” (Ans. 5). The Examiner finds that “Rothwarf et al. teach the importance of phosphorylation of the IKK complex for its kinase activity” (Ans. 5). The Examiner finds that Rothwarf teaches “that the IKK complex can be phosphorylated in vitro by the NIK and MEKK1 proteins to produce an active complex” (Ans. 6).

The Examiner finds that Traincard teaches that “no homologs of any member of the NF- $\kappa$ B signaling system . . . has been found within the genomes of *C. elegans* or *Saccharomyces cerevisiae*” (Ans. 6). The Examiner finds that “Epinat et al. teach that yeast is a convenient host for the reconstitution of the NF- $\kappa$ B system since it does not contain any endogenous NF- $\kappa$ B activity” (Ans. 6).

The Examiner finds it obvious “to reconstitute the IKK complex in a yeast host cells by expressing the IKK subunit genes of Rothwarf et al. in yeast using any known yeast expression vector or yeast expression vectors as taught by Epinat” (Ans. 7).

Appellants contend that

activation of IKK by NIK not only requires NIK to be activated first, but also requires IKK to be in a condition suitable for activation. . . . In the absence of NEMO, IKK is phosphorylated at a serine-rich region of the C-terminus of IKK $\beta$  making it refractory to NIK activation. . . . Therefore, the ‘355 patent teaches that in order for NIK to activate IKK, NEMO needs to be present when IKK is expressed to prevent IKK from being phosphorylated at the serine-rich region of the C-terminus of IKK $\beta$ . NEMO, however, like

other components of the TNF- $\alpha$  and NF- $\kappa$ B signaling pathways, is not present in yeast.

(App. Br. 13).

Appellants contend that “[b]ecause the prior art references do not teach that IKK complex can be phosphorylated and activated by NIK or MEKK1 in the absence of the TNF- $\alpha$  and the NF- $\kappa$ B signaling pathways which yeast lacks, it is not obvious to generate an activated IKK complex in yeast, as prescribed by the claimed invention” (App. Br. 14). Appellants contend that “it is clear that the phosphorylation of IKK by MEKK1 was in the presence of cellular context, rather than in the absence of cellular context” (App. Br. 14).

The issue with respect to this rejection is: Does the evidence of record support the Examiner’s conclusion that Rothwarf, Traincard, and Epinat render obvious claims 2, 23, and 42?

#### Findings of Fact

1. The Specification teaches that “[y]east were transformed and IKK was partially purified by Superose 6 gel filtration. . . .The activity of yhIKK $\beta$  was similar to that of TNF-stimulated HeLa cells” (Spec. 8, ll. 22-27).

2. Rothwarf teaches that “we transfected an expression vector for N-terminally haemagglutinin (HA)-tagged IKK- $\gamma$  into HeLa cells, together with expression vectors for either Flag-tagged IKK- $\alpha$  or Flag-tagged IKK- $\beta$ ” (Rothwarf 298, col. 1).

3. Rothwarf teaches that “IKK- $\alpha/\beta$  can be phosphorylated and activated by over-expressed NF- $\kappa$ B-inducing kinase (NIK) or by MEK

kinase-1 (MEKK-1), but the physiological role of NIK and MEKK-1 in IKK activation by pro-inflammatory cytokines is not clear” (Rothwarf 297, col. 2). (endnotes removed.)

4. Traincard teaches that the “[r]el/NF-κB family of transcription factors and regulators has so far only been described in vertebrates and arthropods . . . No counterparts of genes coding for such proteins have been identified in the *Caenorhabditis elegans* genome and no NF-κB activity was found in *Saccharomyces cerevisiae*” (Traincard 3529, summary).

5. Epinat teaches that in “an effort to identify some of the molecules involved in the activation pathway of NF-κB, we reconstituted part of this system in *Saccharomyces cerevisiae*. We show here that, in a yeast strain harbouring reporter genes controlled by four κB sites, we can mimic the transactivation capacity of p65 and block its activity by coexpression of IκBα” (Epinat 600, col. 2).

6. Epinat teaches that the “yeast *S. cerevisiae* is a convenient host for the reconstitution of the NF-κB system, since it does not contain any endogenous NF-κB activity” (Epinat 603, col. 1).

7. Epinat teaches that these “experiments show that the yeast endogenous kinase pathways cannot modulate NF-κB activity in our system and that p38 kinase does not directly phosphorylate IκBα” (Epinat 608, col. 2).

#### Principles of Law

“The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416 (2007). “If a person of

ordinary skill can implement a predictable variation, § 103 likely bars its patentability.” Id. at 417.

### Analysis

Rothwarf teaches that “we transfected an expression vector for N-terminally haemagglutinin (HA)-tagged IKK- $\gamma$  into HeLa cells, together with expression vectors for either Flag-tagged IKK- $\alpha$  or Flag-tagged IKK- $\beta$ ” (Rothwarf 298, col. 1; FF 2).

Epinat teaches that the “yeast *S. cerevisiae* is a convenient host for the reconstitution of the NF- $\kappa$ B system, since it does not contain any endogenous NF- $\kappa$ B activity” (Epinat 603, col. 1; FF 6).

Applying the KSR standard of obviousness to the findings of fact, we agree with the Examiner that it would have been obvious to express the IKK protein complex in yeast since Rothwarf teaches the desirability of coexpressing all of the IKK complex elements together (FF 2-3) and Epinat teaches that yeast is a convenient host (FF 5-7). Such a combination is merely a “predictable use of prior art elements according to their established functions.” KSR, 550 U.S. at 417.

### Claim 2

Appellants contend that “[b]ecause the prior art references do not teach that IKK complex can be phosphorylated and activated by NIK or MEKK1 in the absence of the TNF- $\alpha$  and the NF- $\kappa$ B signaling pathways which yeast lacks, it is not obvious to generate an activated IKK complex in yeast, as prescribed by the claimed invention” (App. Br. 14). Appellants further contend that the “claimed invention entails separating an activated

IKK protein complex from the yeast which requires that the complex be activated in the yeast” (Reply Br. 11).

We are not persuaded for two reasons. First, as argued by the Examiner (Ans. 8), the claims use the transitional term “comprising” which is open and permits the inclusion of additional steps (see Georgia-Pacific Corp. v. United States Gypsum Co., 195 F.3d 1322, 1327 (Fed. Cir. 1999) (The transitional term “comprising” is “inclusive or open-ended and does not exclude additional, unrecited elements or method steps.”) We disagree with Appellants claim interpretation that the IKK complex must be activated in the yeast. No such requirement is present in claim 2.

Therefore, since Rothwarf teaches the necessary role of NIK and MEKK-1 in activating IKK (FF 3), we agree with the Examiner that inclusion of these molecules, either by cotransfection in the original yeast cell or treatment of the protein after expression in yeast, would have been obvious in order to obtain activated IKK protein (see Ans. 8, 12). Thus, even under Appellants’ claim interpretation requiring activation to occur in the yeast, inclusion of NIK by cotransfection as suggested by Rothwarf would render the claim obvious.

Second, to the extent that yeast cells directly activate the IKK complex as taught by the Specification (FF 1), that represents an inherent property of the yeast cells. It is well established that, as held by a predecessor of our reviewing court:

[I]t is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art. Additionally, where the Patent Office has reason to believe that a functional

limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on. . . . Whether the rejection is based on “inherency” under 35 U.S.C. § 102, on “prima facie obviousness” under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO’s inability to manufacture products or to obtain and compare prior art products. [Citation omitted].

In re Best, 562 F.2d 1252, 1254-55 (CCPA 1977) (footnote omitted); see also In re Spada, 911 F.2d 705, 708 (Fed. Cir. 1990).

Having already determined that it would have been obvious to express the IKK complex in yeast, particularly in light of Epinat’s express teaching that yeast is a convenient system for expression of elements of this specific cellular system (FF 6), the activation of the IKK complex in yeast appears to represent an inherent property possessed by yeast. Appellants have provided no evidence that when the IKK complex members are expressed in yeast, the resulting expressed IKK complex would not inherently satisfy the “activated” requirements of the claim.

Appellants contend that Rothwarf does not teach that NIK or MEKK1 phosphorylates IKK in the absence of any cellular context (see App. Br. 12).

While we agree with Appellants that Rothwarf does not teach performance of the phosphorylation in the absence of any cellular context (that is, in isolated form without cellular proteins), the Examiner reasonably notes that coexpression with the NIK or MEKK proteins in yeast to obtain properly activated proteins would have been obvious (see Ans. 14).

Therefore, we are not persuaded by the Appellants' argument regarding the inclusion of NIK or MEKK1 since these proteins could reasonably be contransfected with the IKK complex proteins to obtain activated IKK complex proteins.

Appellants contend that "NEMO needs to be present when IKK is expressed" (App. Br. 13).

We are not persuaded. As the Examiner points out, NEMO is synonym for IKK $\gamma$ , which Rothwarf teaches should be coexpressed with the other members of the IKK complex (FF 2-3). Consequently, the prior art directly suggests inclusion of IKK $\gamma$  (NEMO) in the yeast expression system (FF 2-7).

#### Claim 42

Appellants contend that "claim 42 was amended to recite that the IKK protein complex is autophosphorylated at a T loop of the IKK subunit beta ( $\beta$ )" (App. Br. 14). Appellants contend that the Examiner "failed to consider (or, at least, comment on) the amendment or the arguments" (App. Br. 15).

The Examiner contends that the "examiner did not . . . specifically comment on claim 42, in isolation from the other claims as the limitations of this claim are met by the cited references in the same fashion as for the previous claims" (Ans. 15). The Examiner contends that the "office Action did point out that the art makes it clear that the phosphorylation produced by NIK is at the site recited in claim 42" (Ans. 15). The Final rejection teaches that "NIK phosphorylates IKK- $\alpha$  on Ser176 and IKK- $\beta$  on Ser177 (i.e., within the T-loop of IKK- $\alpha$  and IKK- $\beta$ )" (Final Rej. 6, 9/2/2009).

We find that the Examiner has the better position. While the Examiner did not identify claim 42 specifically, the Examiner did directly identify a teaching that NIK will inherently phosphorylate the T loop of IKK- $\beta$  which reasonably satisfies the limitation of claim 42. When considering the inherent teachings of a reference, “extrinsic evidence may be considered when it is used to explain, but not expand, the meaning of a reference.” See *In re Baxter Travenol Labs.*, 952 F.2d 388, 390 (Fed. Cir. 1991). Here, the Examiner relies upon Ling simply to teach the inherent result of using NIK to phosphorylate the IKK- $\beta$  protein.

Claim 23<sup>6</sup>

Appellants contend “the Office failed to cite prior art reference disclosing that each IKK subunit protein is a mutated protein (claim 23)” (App. Br. 15).

The Examiner finds that “Rothwarf et al. further teach the production of an IKK complex including a mutant IKK $\gamma$  subunit” (Ans. 5).

Since claim 23 states that “one or more” of the IKK subunits “encodes a mutated IKK subunit protein”, we agree with the Examiner that Rothwarf teaches the use of an IKK subunit which encodes a mutated IKK subunit protein (see Rothwarf, figure 6).

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<sup>6</sup> While MPEP § 707.07(i) only requires that each pending claim and its status is mentioned in each office action, we disagree with the Examiner that it is a waste of time and effort to discuss each dependent claim. Specific identification of the basis of rejection of each dependent claim enhances and improves prosecution by informing Applicants of the specific evidence being relied upon to reject their claims.

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### Conclusion of Law

The evidence of record supports the Examiner's conclusion that Rothwarf, Traincard, and Epinat render obvious claims 2, 23, and 42.

### SUMMARY

In summary, we affirm the rejection of claims 2, 23, and 42 under 35 U.S.C. § 103(a) as obvious over Rothwarf, Traincard, and Epinat. Pursuant to 37 C.F.R. § 41.37(c)(1)(vii)(2006), we also affirm the rejection of claims 5-7, 17-19, 21, and 22, as these claims were not argued separately

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1).

AFFIRMED

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